Remarks

Claims 1-14 and 18-26 were pending. By this amendment, claims 2-4, 9 and 26 are cancelled without prejudice. No claims are added. Therefore, claims 1, 5-8, 10-14, and 18-25 are now pending, with claims 18-25 withdrawn.

Support for the claim amendments can be found throughout the specification, for example page 1, lines 20-21; page 12, lines 18-21; page 14, lines 10-14; page 26, lines 14-20.

No new matter is introduced by this amendment.

Information Disclosure Statements

Applicants note that all of the references listed on page 2 of the specification were cited previously in Information Disclosure Statements and were initialed by the examiner in the September 1, 2009 Office action.

Objections to the specification

The specification was objected to because of informalities, namely because sequences identifiers were not provided on page 17, and certain trademarks were not capitalized. Applicants have corrected these informalities in the specification and provide an updated sequence listing that includes those sequences provided on page 17.

In view of the amendments to the specification made herein, Applicants request that the objection to the specification be withdrawn.

Rejection under 35 U.S.C. §101

Claims 1-14 and 26 are rejected under 35 U.S.C. § 101 on the ground that they do not sufficiently distinguish over antibodies as they exist naturally. Applicants request reconsideration. Claim 1 is amended to recite an "isolated" antibody.

In view of this amendment, Applicants request that the 35 U.S.C. § 101 rejection be withdrawn.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1-13 and 26 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for the recitation "an antibody that 'recognizes' a ... (TRAIL receptor)" because the meaning of the term "recognizes" is unclear. Applicants request reconsideration.

Claim 1 is amended to clarify that the recited TRAIL receptors have a cytoplasmic death domain. Moreover, the Fv units of the claimed antibody are defined to bind to the receptors.

In view of this amendment, Applicants request that the 35 U.S.C. § 112, second paragraph rejection be withdrawn.

Rejections under 35 U.S.C. §112, first paragraph: Enablement

Claims 1-13 and 26 are rejected under 35 U.S.C. § 112, first paragraph on the ground that specification does not reasonably provide enablement for

(i) using any antibody *in vivo* to induce apoptosis in any human cancer subject, and

(ii) antibody fragments having less than the full complement of CDRs or single variable domain antibodies from any TRAIL-R2 antibody. Applicants disagree and request reconsideration.

Claim 26, which relates to a pharmaceutical composition, has been canceled. Thus, the rejection is rendered moot.

Claims 1-13 are directed to "antibodies" rather than "methods of treatment". Thus, whether *in vivo* data are shown for human subjects is irrelevant when determining the enablement of the claimed antibodies. The Examples of the present application demonstrate that the presently claimed antibodies, which comprise at least three Fv units, can be produced and promote apoptosis. That is, the present disclosure provides enablement for the antibodies recited in the pending claims.

Furthermore, claim 1 has been amended to clarify that the antibodies consist of a linker(s) and at least three Fv units. Such antibodies can have H chain-derived three CDRs and four FRs and L chain-derived three CDRs and four FRs for binding to a TRAIL receptor. Thus, "antibody fragments having less than the full complement of CDRs or single variable domain antibodies" are excluded from the amended claims.

Therefore, Applicants request that the 35 U.S.C. § 112, first paragraph rejections be withdrawn.

Rejections under 35 U.S.C. §102

Claims 1, 11 and 26 are rejected under 35 U.S.C. § 102(b) as being anticipated by van Geelen *et al.* (*Br. J. Cancer*, 89(2):363-73, 2003). Claims 1, 11-13 and 26 are rejected under 35 U.S.C. § 102(b)as being anticipated by Ohtsuka *et al.* (*Oncogene*, 22:2034-2044, 2003) and by Ichikawa *et al.* (*Nat. Med.* 7:954-960, 2001). Claims 1-13 and 26 are rejected under 35 U.S.C. § 102(b) as being anticipated by Miller *et al.* (WO 01/77342). Claims 1-5, 9-13 and 26 are rejected under 35 U.S.C. § 102(e) as being anticipated by Li *et al.* (U.S. 2008/0248037). Applicants disagree and request reconsideration.

Enclosed is an English translation of the foreign priority document, JP 2003-415735 (filed December 12, 2003). Thus, Applicants are entitled to their December 12, 2003 priority date.

As discussed above, amended claim 1 is directed to antibodies consisting of a linker(s) and at least three Fv units that bind to a TRAIL receptor. Since the antibodies of van Geelen *et al.*, Ohtsuka *et al.*, and Ichikawa *et al.* are whole antibodies, the pending claims are not anticipated by these documents.

Moreover, the antibodies of Miller *et al.* contain Fc regions or constant region fragments. Miller *et al.* do not disclose "an antibody consisting of a linker(s) and at lease three Fv units". Thus, the amended claims are novel over Miller *et al.*

The present inventors demonstrated that minibodies which recognize TRAIL receptors, and contain at lease three Fv units but not Fc, can be produced and promote apoptosis via multimerization of the TRAIL receptors. These advantageous effects are not disclosed or suggested by the prior art including the above-cited documents. Thus, the presently claimed antibodies are both novel and non-obvious to those skilled in the art over the prior art.

Therefore, Applicants request that the 35 U.S.C. §§ 102(b) and (e) rejections be withdrawn.

If there are any minor issues to be resolved before a Notice of Allowance is granted, the examiner is invited to telephone the undersigned.

Respectfully submitted,

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